Induced Pluripotent Stem Cells for the study of human disorder
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Abstract
In their seminal paper in the August 25, 2006 issue of *Cell*, Takahashi and Yamanaka reported the creation of induced pluripotent stem (iPS) cells from mouse fibroblasts transduced with viral vectors encoding a set of specific transcription factors. This exciting feat was subsequently extended to human cells and has revolutionized our thinking about the analysis and treatment of human disorders. Existing NIH intramural clinical protocols on patients with specific disorders offer a unique opportunity to establish iPS cells from individuals with well characterized genetic disorders. These cells can be used to analyze properties that distinguish them from iPS cells derived from healthy donors. Our laboratories have gained collective experience in the reprogramming of mouse fibroblasts to a pluripotent state, in profiling their karyotypes, transcriptomes and epigenomes, and in establishing various differentiated derivatives from these cells. Our current experiments are focused on the isolation and molecular characterization of human iPS cells. Currently available methods of reprogramming will be adjusted, as needed to incorporate the latest advances in the field. This will include testing reprogramming abilities of small molecules active in chromatin modification, another collective expertise of our laboratories. The resulting iPS cells will be utilized in the context of an innovative project aimed at generating novel tools for ongoing intramural NIH studies of specific genetic disorders. In the two-year time frame of this grant application, we propose to generate iPS cell lines from a number of patients selected from a number of cohorts, including, but not limited to, Smith-Lemli-Opitz Syndrome, Niemann-Pick Disease and Chediak-Higashi disease. A separate project will use iPS technology to analyze the characteristics of the human leukemia stem cell. We expect to generate a panel of iPS cell lines from patients and healthy donors and to arrive at comparable denominators of their expression profiles and those of specific differentiated derivatives. The ultimate goals of our work go well beyond the generation of human iPS cells described in this application and are geared towards research on patient-specific gene de-regulation. Furthermore, we plan to use these cells in high throughput drug screens aimed at the identification of potential therapeutic agents. Finally, we are interested in developing future strategies of patient-specific cell therapy.